REMARKS

Applicant expresses his appreciation to Examiner Pryor for the courtesy of an interview which was granted to Applicant's representative, Sanford T. Colb (Reg. No. 26,856). The interview was held in the USPTO on June 25, 2002. The substance of the interview is set forth in the Interview Summary, Paper No. 8.

Applicant has carefully studied the outstanding Official Action. The present amendment is intended to be fully responsive to all issues raised by the Examiner and is believed to place the application in condition for allowance. Favorable reconsideration and allowance of the application are respectfully requested.

Claim 2 has been amended to independent form. Claim 3 has been amended to clarify that the steps recited therein recite a particular way of carrying out the step of mixing the dry micronized progesterone with a pharmaceutically acceptable non-effervescent excipient or diluent therefor and an effervescent, which is recited in claim 2. Claims 8 and 36 have been amended to correct the dependencies therein.

New claims 46-54 have been added to recite methods of treatment which utilize tablets prepared in accordance with the present invention. New claim 51 has been added to recite a vaginally administrable tablet containing micronized progesterone, an effervescent, and a non-effervescent excipient or diluent. New claims 52-54 have been added to recite methods of treatment which utilize the tablet of claim 51. These claims are supported, *inter alia*, by paragraphs 58-72 of the application.

Claims 1-43 stand rejected under 35 U.S.C. §112, second paragraph as being indefinite for reciting the terms "substantially 0%" and "substantially dry". Claims 1, 2, 40 and 41 have

been amended to recite "drying said wetted micronized progesterone to form dry micronized progesterone". It is thus respectfully submitted that the basis for this rejection has been obviated.

Claims 2 and 41, which have now been amended to independent form, stand rejected under 35 U.S.C. §112, second paragraph as being indefinite for reciting the terms excipients and diluents as being distinct from an effervescent. The effervescent recited in claims 2 and 41 is present to assist in the disintegration of the tablet in body (as will be explained more fully below), and thus is intended to be distinct from the excipient or diluent recited in the claims. To help clarify this distinction, claims 2 and 41 have now been amended so as to make clear that the effervescent recited in claims 2 and 41 is distinct from the excipient or diluent recited in these claims. It is thus respectfully submitted that the rejection of claims 2 and 41 under 35 U.S.C. §112, second paragraph has now been overcome.

Claims 13-15 stand rejected under 35 U.S.C. §112, second paragraph as being indefinite for using the terms "Cornstarch 1500" and "Povidone", since it is asserted that these terms are trademarks which do not describe or identify the goods but rather the source of the goods. Applicant respectfully disagrees. The term "povidone" is not a trademark but rather, according to the World Health Organization, a generic term for polyvinylpyrrolidone. Please see the enclosed printout, taken from the website of the Joint Expert Committee on Food Additives of the World Health Organization, available online at (http://jecfa.ilsi.org/evaluation.cfm?chemical=POLYVINYLPYRROLIDONE&keyword=POVIDONE). The term "Povidone 30" has been corrected to recite the proper term "Povidone K-30". As to "Cornstarch 1500", Applicant concurs that the term "Starch 1500" is a registered trademark for a particular brand of partially pregelatinized maize (corn) starch. See http://www.colorcon.com/translated_literature/Starch_1500/English.pdf. Applicant has amended claim 13 to recite "cornstarch" rather than "Cornstarch 1500".

Claims 1-9,11-26 and 33-45 stand rejected under 35 U.S.C. §103(a) as obvious over either of the Greco et al. patents (US 5,084,277 and US 5,116,619). Applicant respectfully submits that the present invention is not obvious in view of either Greco et al. publication

The background against which the present invention was developed was that in certain circumstances, it is desirable to deliver progesterone directly into the bloodstream (rather than by metabolism of progesterone or a progesterone precursor in the liver), thereby achieving a systemic effect, by administering progesterone via the vagina. While vaginal drug delivery systems are known in the art, few such systems are directed toward achieving systemic effects.

Furthermore, it is considered desirable to use micronized progesterone, i.e. progesterone which has been very finely ground. For example, an orally administrable form of progesterone, Solvay Pharmaceuticals' Prometrium® capsules, utilizes micronized progesterone to improve absorption in the body. However, micronized progesterone normally has particular bulk physical properties which tend to make vaginal administration, as opposed to oral administration, difficult. Among other things, micronized progesterone is not sufficiently free-flowing to enable the tabletting of progesterone by so-called direct-compaction methods. If the amounts of progesterone required were smaller--say, 3 mg per 1000 mg tablet--it might be possible to employ direct compaction. However, in order to achieve systemic effects, it is necessary that the tablets contain substantially larger amounts of micronized progesterone per tablet, on the order of 75 ± 25 mg or more per 1000 mg tablet. Given the bulk properties of micronized progesterone, the inclusion of such amounts of micronized progesterone cannot be achieved using direct compaction methods.

The Greco et al. patents disclose a vaginal drug delivery system designed to release progesterone in a manner that achieves a systemic effect. However, the process that Greco et al. use to obtain their tablets involves wet granulation of the progesterone, i.e. a process in which the progesterone and other ingredients are mixed while wet and then dried and compacted. See, e.g., Example 2 of the '619 patent, which explains at col. 6, lines 54-56 that after micronized progesterone was mixed with lactose and starch paste, "the damp mass was then passed through a number 12 screen and the granules were dried for 3 hours at 50°C. The moisture content at this point was less than 1%." See also col. 8, lines 30-33 of the '619 patent. As is well-known in the art, wet granulation processes necessitate several steps in the formulation of the resulting tablets, such as the need for additional screening or sieving (i.e. granulation) steps. See e.g. col. 8, lines 30-36 of the '619 patent. These additional steps add considerably to the production costs of the tablets produced thereby in comparison to comparable direct compaction methods.

With the present invention, the inventor discovered a way to form vaginally administrable progesterone-containing tablets by direct compaction, in which the ingredients are mixed and directly compacted in dry form. Not only do Greco et al. give no suggestion as to how one might be able to tablet progesterone via a direct-compaction method, which is economically more desirable, but Greco et al. explicitly teach away from a direct-compaction method. See Example 14 of Greco et al., which explains that when Greco et al. attempted to prepare tablets by a dry technique (referred to Example 14 as a "recompression" technique, which, in contrast to the preparative technique described in Example 2 of Greco et al., did not use aqueous media), the tablet obtained "was inferior to the tablets prepared by the method of Example 2. The recompressed tablet rapidly decomposed after insertion in the human vagina..." ('619 patent, col. 10, lines 14-18.)

With the presently claimed invention, the inventor discovered a means for affecting the flow properties of micronized progesterone so as to render the progesterone amenable to direct-compaction methods. This is reflected in the claims in the requirement for the wetting and drying of the progesterone prior to mixing the progesterone with the other ingredients. Failure to observe this wetting/drying protocol in a direct-compaction process would result in the inability to form tablets having the necessary properties, as evidenced by Greco et al.

It is Applicant's understanding that the Examiner believes Examples 4-6 of Greco et al. demonstrate a means of rendering micronized progesterone suitable for use in direct compaction, by first mixing the micronized progesterone with wet cornstarch ("cornstarch paste", see e.g. col. 7, lines 34-38 of the '619 patent), drying this mixture, and then mixing the material obtained with the remaining ingredients and forming tablets. Applicant respectfully submits that this example does not teach or suggest the presently claimed invention. First, Greco et al. report in Example 2 that the disintegration time of the tablet prepared by wet granulation was 4-6 minutes in water using the USP XXI (Physical Test 701) test and 6-8 hours in the vagina (col. 7, lines 17-20 of the '619 patent). In contrast, the tablets prepared in examples 4-6 of Greco et al. are reported as having a dissolution time in water of 43 seconds or less using the same USP XXI (Physical Test 701), and no vaginal dissolution time is reported. Given that at column 14, lines 14-23, tablets prepared by "recompression" and having a dissolution time of 60-90 seconds are reported as being unsuitable for *in vivo* use, it is respectfully submitted that the tablets prepared in accordance with Examples 4-6 of Greco et al., which have significantly shorter dissolution times in water, are even more unsuitable for vaginal adminstration.

Second, in point of fact, the inventor of the present invention attempted to prepare tablets in a manner similar to that reported in Examples 4-6 of Greco et al., but using polyvinylpyrrolidone rather than "corn starch paste" as the binder. The inventor mixed

micronized progesterone with an aqueous solution of PVP, and then dried and granulated this mixture prior to mixing with the remaining ingredients and compacting. This was found to yield unsatisfactory results: the size of the micronized progesterone/PVP granules proved to be too large to mix with the remaining ingredients to obtain a sufficiently homogenous mixture for compaction for use as a tablet (just as one would not obtain a uniform salt dispersion in a mixture of dry table salt and dry flour, because of size differences in the particles).

Also, the inventor attempted to prepare tablets by a wet compaction method, similar to that of Greco et al., but it was found that in a significant percentage of cases, in women undergoing in vitro fertilization (IVF) treatment the tablets so prepared either left particulate matter in the vagina, which was uncomfortable for the patients in whom this occurred, or did not dissolve, which was not only uncomfortable and necessitated removal of undissolved tablets by the attending physician but also meant the progesterone did not reach the endometrium of the patient.

Submitted concomitantly with this response are Rule 132 declarations (fax copies) from the inventor and from a physician who is the head of one of the world's leading IVF units. These declarations attest to the fact that tablets prepared by wet granulation akin to Greco et al. were unsatisfactory because they left particulate matter in a significant percentage of patients undergoing IVF treatment, whereas this drawback was overcome using tablets according to the present invention. The affidavit of the inventor also attests to the fact that an attempt to first mix micronized progesterone and wet PVP before mixing with other ingredients, in a manner similar to that of Examples 4-6 of Greco et al., resulted in unsuitable tablets. The declaration of the inventor also attests to the fact that direct compaction of the ingredients without first wetting and drying the micronized progesterone did not yield vaginally adminstrable tablets.

It is thus respectfully submitted that claims 1 and 40 are not obvious in view of the Greco et al. patents. Likewise, those claims which depend directly or indirectly from claims 1 and 40 are believe to be patentable over the Greco et al. patents.

With respect to claims 2 and 41, it transpires in some cases that the vagina of the patient is insufficiently dry to enable good dissolution of the tablet. Consequently, in order to improve the dissolution of progesterone-containing tablets in the vagina of such women, it may be preferable to include an effervescent in the tablets, in order to aid dissolution of the tablets. Direct compaction allows the ingredients required to produce an effervescent effect (e.g. bicarbonate and an acid) to be incorporated into the tablets. For obvious reasons, the effervescent components cannot be incorporated into the tablet using wet granulation or any other process that will allow the components of the effervescent to react. Just as trying to make an Alka-Seltzer® tablet in water would be self-defeating, so too is trying to form progesterone tablets containing an effervescent using a wet-granulation process.

Moreover, mixing and compacting an effervescent with dry, granulated ingredients which have already been mixed by wet granulation and then dried is not feasible. This is because the components of the effervescent would be much smaller than the progesterone-containing granules previously formed by wet granulation, and thus it would not be possible to obtain a sufficiently homogenous mixture of effervescent and the remaining ingredients to produce tablets with a consistent progesterone release profile.

Moreover, as can be seen for example at col. 12, lines 27-61 of Greco et al's '277 patent, Greco et al. achieve maximum progesterone concentration in the blood an average of 23.3 hours after administration. Thus even if an effervescent could be incorporated into the tablets of Greco et al, such incorporation of an effervescent would lead to faster dissolution of the tablets than is

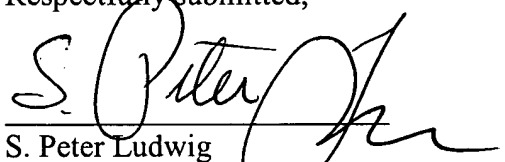
the stated goal of Greco et al. See e.g. col. 3, lines 37-38 of the '277 patent: "It is therefore an object of this invention to provide a vaginal tablet having prolonged bioavailability". In other words, even if an effervescent could be included in the tablets of Greco et al., such inclusion would render the invention of Greco et al. inoperable. It is therefore respectfully submitted that Greco et al. thus teach away from the present invention as claimed in claims 2 and 41.

Thus the method of claim 2 and the tablets of claims 41 and 51 are not obvious in view of Greco et al., since the teaching of Greco et al. cannot be used to produce tablets containing an effervescent.

It is thus respectfully submitted that claims 2 and 41, as well as new claim 51, are patentable over Greco et al., and that consequently the claims which depend directly or indirectly from claim 2 or 41 are likewise patentable.

In view of the foregoing amendments and remarks, all of the claims are believed to be allowable. Favorable reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,



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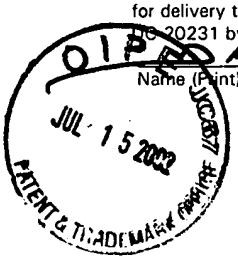

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of : Azariah JOSSIFOFF

Serial No. : 09/856,417, National Phase of PCT/IL99/00619, Filed Nov. 17, 1999

Filed : August 8, 2001

For : VAGINALLY ADMINISTRABLE PROGESTERONE-CONTAINING TABLETS AND METHOD FOR PREPARING SAME

Group Art Unit: 1616
Examiner: Alton Pryor

Hon. Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

MARKED-UP COPY OF CLAIMS PER 37 C.F.R. §1.121(c)(1)(ii)

1. (Amended) A method for preparing a tablet for the vaginal administration of progesterone for systemic use, comprising the steps of:

slowly mixing water with micronized progesterone, the total amount of water mixed with said micronized progesterone not exceeding the maximum wetting capacity of the amount of micronized progesterone, whereby to obtain wetted micronized progesterone;

drying said wetted micronized progesterone to [a humidity content of substantially 0%, whereby to] form [substantially] dry micronized progesterone;

mixing said [substantially] dry micronized progesterone with [other] a pharmaceutically acceptable [excipients] excipient or [diluents] diluent therefor; and

forming a tablet by direct compaction of said [substantially] dry micronized progesterone which has been mixed with said [other] pharmaceutically acceptable [excipients] excipient or [diluents] diluent therefor.

2. (Amended) A method [according to claim 1] for preparing a tablet for the vaginal administration of progesterone for systemic use, comprising:

slowly mixing water with micronized progesterone, the total amount of water mixed with said micronized progesterone not exceeding the maximum wetting capacity of the amount of micronized progesterone, whereby to obtain wetted micronized progesterone;

drying said wetted micronized progesterone [to a humidity content of substantially 0%, whereby] to form [substantially] dry micronized progesterone;

mixing said [substantially] dry micronized progesterone with (a) [other] a pharmaceutically acceptable non-effervescent [excipients] excipient or [diluents] diluent therefor [, including] and (b) an effervescent; and

forming a tablet by direct compaction of said [substantially] dry micronized progesterone which has been mixed with said [other] pharmaceutically acceptable non-effervescent [excipients] excipient or [diluents] diluent therefor [, including] and said effervescent.

3. (Amended) A method according to claim 2 for preparing a tablet for the vaginal administration of progesterone for systemic use, [comprising] wherein the [steps] step of mixing said dry micronized progesterone with (a) a pharmaceutically acceptable non-effervescent excipient or diluent therefor and (b) an effervescent comprises:

[slowly mixing water with micronized progesterone, the total amount of water mixed with said micronized progesterone does not exceed the maximum wetting capacity of the amount of micronized progesterone, whereby to obtain wetted micronized progesterone;

drying said wetted micronized progesterone to a humidity content of substantially 0%, whereby to form substantially dry micronized progesterone;]

sieving a first lubricant to obtain a sieved first lubricant;

mixing said [substantially] dry micronized progesterone with said sieved first lubricant and a material selected from a first filler or a disintegrant to form a first mixture;

mixing a binder which binds dry particles with said first mixture to form a second mixture;

intimately mixing [an] said effervescent and a first quantity of a second filler to form a third mixture;

sieving said third mixture to obtain a sieved third mixture, and then intimately mixing said sieved third mixture and said second mixture to form a fourth mixture;

intimately mixing said fourth mixture with a second quantity of said second filler to form a fifth mixture;

sieving a second lubricant and a material selected from a saponificant or a third lubricant to obtain, respectively, sieved second lubricant and sieved third lubricant; and

intimately mixing said sieved second lubricant and said sieved third lubricant with said fifth mixture to form a sixth mixture[; and

tabletting said sixth mixture by direction compaction to form a tablet].

8. (Amended) A method according to claim [1] 3 wherein said sieved second lubricant and said sieved third lubricant are sieved through sieves having a pore size of between about 100 and 150 microns.

13. (Amended) A method according to claim 12 wherein said starch is cornstarch [1500].

14. (Amended) A method according to claim 3, wherein said binder which binds dry particles is polyvinylpyrrolidone [(povidone)] (Povidone).

15. (Amended) A method according to claim 14, wherein said binder which binds dry particles is Povidone K-30.

36. (Amended) A method according to claim 1, wherein said water is added to said micronized progesterone at rate of between about 6 to 9 ml per minute.

40. (Amended) A tablet prepared by the steps of:

slowly mixing water with micronized progesterone, the total amount of water mixed with said micronized progesterone not exceeding the maximum wetting capacity of the amount of micronized progesterone, whereby to obtain wetted micronized progesterone;

drying said wetted micronized progesterone to [a humidity content of substantially 0%, whereby to] form [substantially] dry micronized progesterone;

mixing said [substantially] dry micronized progesterone with [other] a pharmaceutically acceptable [excipients] excipient or [diluents] diluent therefor; and

forming a tablet by direct compaction of said substantially dry micronized progesterone which has been mixed with said [other] pharmaceutically acceptable [excipients] excipient or [diluents] diluent therefor.

41. (Amended) A tablet prepared by the steps of:

slowly mixing water with micronized progesterone, the total amount of water mixed with said micronized progesterone not exceeding the maximum wetting capacity of the amount of micronized progesterone, whereby to obtain wetted micronized progesterone;

drying said wetted micronized progesterone [to a humidity content of substantially 0%, whereby] to form [substantially] dry micronized progesterone;

mixing said [substantially] dry micronized progesterone with (a) [other] a pharmaceutically acceptable non-effervescent [excipients] excipient or [diluents] diluent therefor [, including] and (b) an effervescent; and

forming a tablet by direct compaction of said [substantially] dry micronized progesterone which has been mixed with said [other] pharmaceutically acceptable non-effervescent [excipients] excipient or [diluents] diluent therefor [, including] and said effervescent.

46. A method of delivering progesterone to a female patient, comprising placing in the vagina of said patient a tablet as recited in claim 40 and retaining said tablet in said vagina for a time efficacious to deliver said progesterone to said patient.

47. A method according to claim 46, wherein said tablet contains at least 50 mg of micronized progesterone.

48. A method of delivering progesterone to a female patient, comprising placing in the vagina of said patient a tablet as recited in claim 41 and retaining said tablet in said vagina for a time efficacious to deliver said progesterone to said patient.

49. A method according to claim 48, wherein said tablet contains at least 50 mg of micronized progesterone.

50. A method according to claim 48, wherein said placing of tablet is effected as part of a twice-daily dosing regimen.

51. A vaginally administrable tablet comprising micronized progesterone, a non-effervescent excipient or diluent therefor, and an effervescent.

52. A method of delivering progesterone to a female patient, comprising placing in the vagina of said patient a tablet as recited in claim 51 and retaining said tablet in said vagina for a time efficacious to deliver said progesterone to said patient.

53. A method according to claim 52, wherein said tablet contains at least 50 mg of micronized progesterone.

54. A method according to claim 53, wherein said placing of tablet is effected as part of a twice-daily dosing regimen.